The need for continuous quality assessment for providing optimal comprehensive care for patients with alpha-1 antitrypsin deficiency

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ABSTRACT

Background: *Alpha-1-antitrypsin deficiency (AATD) is an orphan disease that mainly affecting the liver and the lung. This creates difficulties to ensure that comprehensive care is administered to both organ systems. Past assessments of care delivered to patients with AATD demonstrated that improvements are needed. For that reason, we reassessed a population of patients with AATD in a large health care system to see if past findings affected present care.*

Methods: *We performed electronic health record (EHR) reviews on all patients with documented AATD and confirmed the diagnosis by evidence of genotyping. We then selected the patients with the ZZ genotype to review comprehensive care. We further compared the findings in patients treated by different specialists (allergy immunology, gastroenterology, and pulmonary). The data were captured and assessed by using a secure web application for building and managing online surveys and data bases. REDCap.*

Results: *We found a total of 329 patients with diagnostic codes for AATD, of these, 203 patients had a confirmed abnormal genotype. Confirmed genotypes were MZ (n = 69), ZZ (n = 48), MS (n = 22), SZ (n = 22). Further focus was applied to the care of the ZZ population secondary to a predisposition to potential severe lung and liver disease. The findings suggest that care can be improved no matter which specialist cares for the patient.*

Conclusion: *Our study demonstrated that all three subspecialty groups had room for improvement in providing care to patients with AATD. Our study further demonstrated the need for recurrent quality-assurance programs that may be aided by care suggestions built into the EHR.*

(Allergy Asthma Proc 42:537–542, 2021; doi: 10.2500/aap.2021.42.210067)

Alpha-1 antitrypsin (AAT) is a glycoprotein encoded by SERPINA1, which is produced in the liver[1] and functionally inhibits neutrophil elastase in the airways and other organs.[2] The normal form of the protein is considered the M type, which is the most common form of the protein.[2] Low amounts of AAT are associated with AAT deficiency (AATD). The clinical presentation of AATD is variable; although, most commonly, patients present with dyspnea, cough, or wheezing associated with early onset emphysema.[3] Of the mutant variants, the Z type protein is the most common, followed by the S, null, and F variants.[2] If a defective protein is inherited, then low or absent levels of the AAT protein may be found in serum, which results in AATD. Clinical manifestations of AATD include emphysema, liver disease, necrotizing panniculitis, and a c-antineutrophil cytoplasmic antibodies (C-ANCA) positive vasculitis.[2,4,5] AATD affects all races worldwide; however, the highest prevalence is in northwestern Europe.[4,6] The frequency of mutant carrier proteins is 2–3% in Americans.[4,6]

Although AATD is described as a rare condition, it is underdiagnosed, with only 10% of patients being identified, with delays of >5 years between the initial symptom onset and the diagnosis.[5,7–10] Patients have a delayed or no diagnosis due to genetic and clinical heterogeneity, low recognition of the disease, and the complexity of the diagnosis.[4] A delayed diagnosis of AATD hinders the initiation of disease management, such as protein augmentation; patient education with regard to smoking and alcohol use; preventative treatments, including vaccinations; and genetic counseling.[7] The Medical and Scientific Advisory Committee of the Alpha-1 Foundation recommend that all patients with COPD, asthma with fixed obstruction, unexplained chronic liver disease, necrotizing panniculitis,

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This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1 TR002014 and grant UL1 TR00045. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

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unexplained bronchiectasis, or a family history of abnormal AAT undergo quantitative protein screening[11]; if quantitative screening is abnormal, then genotype testing should be completed to properly diagnose individuals with AATD.[10,12]

Although AATD provokes both lung and liver dysfunction, the current understanding suggests independent disease pathogenesis between organ systems.[1] Normally, AAT inhibits elastase in the lung, which protects against alveolar degradation. Diminished functioning of AAT disrupts proper protease-antiprotease relationships, which allow unopposed destruction of the lung matrix and alveolar architecture. For this reason, patients with AATD are at increased risk of developing COPD, especially when concurrent exposures to additional factors that increase elastase production, such as cigarette use and infection, are present.[3] The Z variant causes marked reduction in circulating AAT levels, and the S variant protein causes only slight reduction in AAT levels; although the F variant can have normal levels of protein, it is a dysfunctional protein.[13] For this reason, most experts recommend testing protein and genotypes to ensure a proper diagnosis. The ZZ subtype is the most severe form of AATD because the abnormal shape of the protein causes liver disease and the low amounts of functional protein manifests as lung disease.[12] Liver disease is caused by polymerization of the misfolded mutant Z protein, which leads to retention inside the hepatocyte.[1,10] Accumulation of the Z protein within hepatocytes incites hepatocellular death and liver damage, which results in a variable clinical presentation, including chronic hepatitis, cirrhosis, hepatocellular carcinoma, or, rarely, fulminant hepatic failure.[1,10] Because AATD has broad severe complications, it is essential to monitor and manage patients with AATD holistically.

The goal of this study was to perform quality assurance for patients with AATD in a large academic health-care system to determine if comprehensive care was being provided. Years before this project, we assessed care provided to patients with AATD in the same health-care system and found many opportunities for improvement; however, persistence of these improvements has not been assessed.[11] Quality assurance is essential at all levels of health-care systems and provides just one aspect of the constant, continual process required to optimize patient care and outcomes.[14] For this quality assurance, we sought to determine if the physicians were ordering appropriate tests, vaccinations, and medications as well as appropriately counseling their patients with AATD. Because multiple types of providers, including allergists, gastroenterologists, and pulmonologists, are the primary physicians for treating AATD in patients, we then analyzed the proficiency for treating AATD of each type of specialist.

METHODS

The study was of quality assurance, and met exclusion criteria for Penn State University IRB approval. An electronic health record (EHR) search provided patients with diagnostic coding for AATD from one academic health-care center where we are associated. Each chart was reviewed to confirm an abnormal AAT genotype. Each chart was then reviewed for the following aspects of the patient and his or her care when using recommendations from the Medical and Scientific Advisory Committee of the Alpha-1 Foundation[12]: demographics, genotype of AATD, specialty of the AATD-managing provider, current tobacco use, annual spirometry testing, annual liver function tests, annual abdominal ultrasound or computed tomography (CT), one-time CT of the chest, up-to-date PPSV23 (pneumococcal polysaccharide vaccine) and PCV13 (pneumococcal conjugate vaccine) (PCV13 is not recommended by the Centers for Disease Control and Prevention until age 65 years for COPD), hepatitis A and B vaccination, annual influenza vaccination, AAT protein augmentation, inhaled corticosteroid (ICS), albuterol, long-acting β-adrenergic agonist (LABA), pulmonary rehabilitation referral, tobacco use education, and alcohol use education. For annual aspects of care, the past 5 years were referenced in the patients' charts.

Once collected, the data were analyzed by separating the genotypes. For the ZZ genotype, the data were further analyzed by provider specialty for the aspects of patient care. Patients with the ZZ genotype but who were cared for by pediatric specialists, primary care providers, or other specialists were excluded from the analysis. Patients who were deceased or had not been evaluated by a physician at the health-care system for 5 years before the time of analysis were also excluded. Percentages were calculated for the patients who received each appropriate aspect of management. Study data were collected and managed by using REDCap[15] (Research Electronic Data Capture) electronic data capture tools hosted at Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine. REDCap[15] is a secure, web-based application designed to support data capture for research studies and provides (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, and (3) automated export procedures for seamless data downloads to common statistical packages procedures for importing data from external sources.

RESULTS

The EHR search provided a total of 329 patients with diagnostic codes for AATD (Fig. 1). After reviewing each chart, 203 patients had a confirmed abnormal genotype. We selected the genotype instead of protein levels, secondary to "α-protein" being an acute

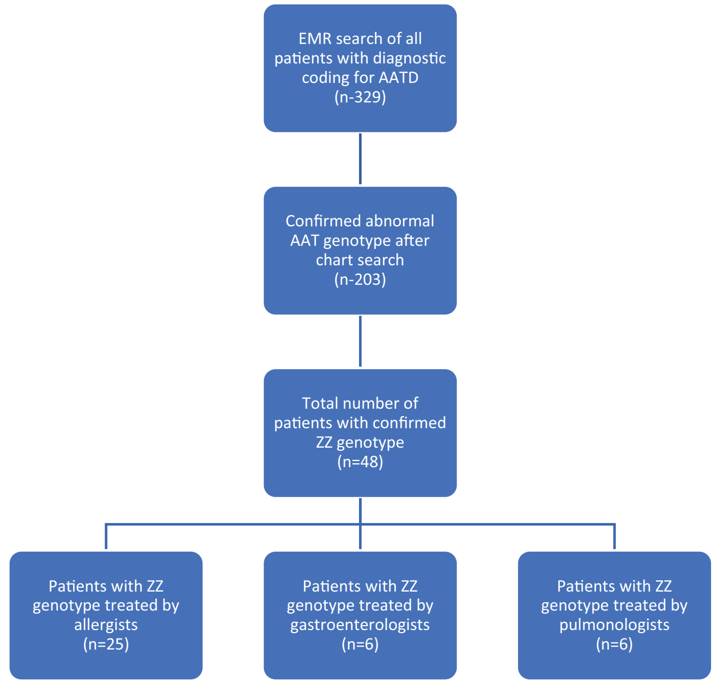

Figure 1. *Summary of the number of patients used for analysis. Aspects of care for the patients with the ZZ genotype treated by allergists, gastroenterologists, and pulmonologists were analyzed.*

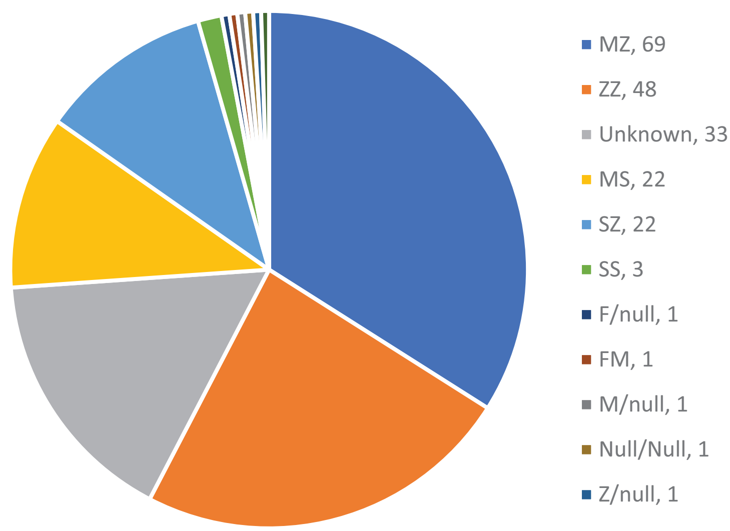

Figure 2. *Depiction of the spread of genotypes was determined from the total number of confirmed abnormal genotypes (genotype, n). For the unknown, the patient had confirmed abnormal genotype, but the test results were not available in the electronic health record (EHR).*

inflammatory protein and because of overlap of different genotypes with protein levels, and this may have excluded most of the 126 patients that add low protein levels, but no genotype. In some cases, the genotyping was done with probes limited to S and Z and thus some of the rarer genotypes may have been missed. The most common abnormal genotype was MZ, and 69 patients with the MZ genotype were managed within the health-care center (Fig. 2). Other genotypes were ZZ (n = 48), MS (n = 22), and SZ (n = 22) (Fig. 2). Rarer types, including null and F variants, were also treated. Some patients were considered "unknown" genotypes due to reports of abnormal genotypes, but laboratory results or specific genotypes were not confirmed in their patient chart. Due to the severity and complexity of the ZZ genotype, their management was further analyzed, which provided a total of 48 patients in the health-care system. Allergy, asthma, and immunology; gastroenterology; or pulmonology providers managed 37 patients with ZZ genotype of AATD.

Allergists provided care for 25 patients with AATD, whereas gastroenterologists and pulmonologists cared for 6 patients each (Fig. 1). Of all patients with the ZZ genotype, only one used tobacco products as last noted in his or her chart. In terms of testing, yearly spirometry, yearly liver function tests, yearly abdominal ultrasound

Table 1 **Demographic, testing, vaccination, medication, education, and referral data for patients with the ZZ genotype by specialty***

	Allergists	Gastroenterologists	Pulmonologists	*p*#
Demographics				
No. patients	25	6	6	
Mean age of patients, years	60.73	54.69	65.05	0.302§
Men/women, *n*	11/14	4/2	3/3	0.705
Current tobacco use, %	0.00	16.67	0.00	0.329
Testing, %				
Spirometry (yearly)	56.00	0.00	83.33	0.006
LFT (yearly)	48.00	33.33	50.00	0.879
Liver US and/or CT (yearly)	40.00	50.00	33.33	0.897
Chest CT (once)	68.00	16.67	83.33	0.023
Vaccination, %				
PPSV23	88.00	16.67	100.00	<0.001
PCV13	88.00	16.67	83.33	0.001
Influenza	96.00	33.33	100.00	<0.001
Hepatitis A and B	92.00	83.33	100.00	0.553
Medication, %				
Augmentation	48.00	0.00	16.67	0.049
Inhaled corticosteroid	68.00	33.33	50.00	0.173
LABA	56.00	0.00	66.67	0.038
Anticholinergic	52.00	0.00	83.33	0.006
Albuterol	64.00	16.67	100.00	0.007
Education and referral, %				
Pulmonary rehabilitation referral	36.00	0.00	66.67	0.076
Alcohol education	88.00	100.00	100.00	1.000
Tobacco education	88.00	83.33	100.00	0.558

LFT = ; US = ultrasound; CT = computed tomography; PPSV23 = pneumococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; LABA = long-acting β–adrenergic agonist.
**Data are depicted as the percentage of patients who have documentation for each component of α-1-antitrypsin deficiency management.*
#χ^2 test; significant if $p < 0.05$.
§Kruskal-Wallis test was used.

or CT, and a one-time CT occurred for 56, 48, 40, and 68% of allergists' patients, respectively (Table 1). In addition, allergists' patients had high levels of up-to-date vaccinations for pneumococcal vaccinations (88% "pneumococcal polysaccharide vaccine", 88% "pneumococcal 13-valent conjugate vaccine"), hepatitis (96%), and influenza (92%). For medications, a majority of allergists' patients were prescribed ICS, LABAs, anticholinergics, and albuterol. Forty-eight percent of the patients used α-1 protein augmentation. In addition, allergists had documented counseling of 88% of their patients for alcohol and tobacco use. However, allergists only referred 36% of their patients to pulmonary rehabilitation. Because of the limited availability and access to pulmonary rehabilitation, this may not have been a logical outcome to use.

As noted, we also assessed gastroenterologists and pulmonologists who treated patients with AATD. Pulmonologists ordered appropriate testing to include yearly spirometry, yearly liver function tests, yearly ultrasound or CT of liver, and one time chest CT (83.33, 50.00, 33.33, 83.33%), up-to-date vaccinations to include both pneumococcal, hepatitis and influenza (100, 83.3, 100, 100%), prescribed medications to include ICS, LABAs, LAMAs and albuterol (16.67, 50.00, 66.67, 83.33, 100.00%), and educated patients about tobacco (100%) and alcohol use (100%) (Table 1). Gastroenterologists have lower rates of testing (0.00, 33.33, 50.00, 16.67%), vaccination (16.67, 16.67, 33.33, 83.33%), and prescribing medications to their patients (0.00, 33.33, 0.00, 0.00%, 16.67%) (Table 1). Various specialists had significantly different rates of annual spirometry, one-time CT of the chest, PCV13 vaccination, PPSV23 vaccination, protein augmentation, LABA, ICS, and albuterol use when using a χ^2 analysis (Table 1). We included the use of pneumococcal conjugate vaccine (PCV-13) in COPD before age 65 years and realize that this is controversial and not recommended by the Centers for Disease Control and Prevention; however, the Alpha-1 Foundation[12] does suggest administration of PCV13.

DISCUSSION

AAT is an underdiagnosed condition with various clinical presentations and genetic heterogeneity.[7] The disease follows codominant inheritance, and two different variants of the gene may be expressed.[2] This is important because MZ genotypes are susceptible to hepatic and lung disease, however, not to the extent of ZZ or null genotypes.[2] Most importantly, only 10% of patients with severe AATD, mainly those with the ZZ genotype, have been diagnosed.[7] For this reason, the most important part of care for AATD is to test for the disease to identify those who require care. The American Thoracic Society suggests that all patients with COPD, asthma that has a component of fixed airway disease, unknown bronchiectasis, unknown liver disease, panniculitis, and ANCA positive vasculitis be screened for AATD.[11] Allergists, because they care for many patients with obstructed lung disease, should be screening for AATD[2] as per the American Thoracic Society guidelines. The diagnosis is the key component to providing care.

As determined through this quality-assurance review, allergists can be proficient in managing patients with AATD, but analysis of our data suggests that there is much room for improvement. This study demonstrated that the MZ genotype is the most common variant of AATD, followed by the severe ZZ genotype in the Penn State Health system, which has previously been described (Fig. 2).[3,5,8] One health-care system provided care for 48 patients with the ZZ genotype of AATD, and allergists, gastroenterologists, and pulmonologists took care of 25, 6, and 6 patients, respectively (Fig. 1). Because the ZZ genotype causes both liver and lung disease,[1–3,10] multifactorial, multispecialty, and multisystem monitoring and managing should be considered for patients with severe AATD.

Allergists seem to demonstrate the competency to treat patients holistically with AATD, specifically, the severe ZZ genotype, at a large academic health center. Nonetheless, our quality-care project demonstrated the need for improvement in all three specialties studied. Because cigarette use increases the risk of COPD[3] and no patients cared for by allergists used tobacco (Table 1), the allergists seemed to effectively counsel their patients about tobacco use. Moreover, allergists are capable of managing patients with complex treatment regimens, including injectables, as evident for the care provided to patients with primary immunodeficiency and hereditary angioedema. Many self-injectable medications and home-injected medications infused by nurses as well as infusion center care are prescribed and arranged by allergists, so allergists are equipped to manage patients with AATD who require α-1 protein replacement, often referred to as augmentation.

According to the Medical and Scientific Advisory Committee of the Alpha-1 Foundation, multiple aspects of patient care should be monitored and managed.[12] Although the results of this study suggested that allergists can be proficient in caring for patients with severe-type AATD, increased education and awareness about AATD can improve patient outcomes. Quality assurance is one step in improving care for patients by bringing awareness to the successes and shortcomings of patient care for physicians. AATD is relatively new to the allergist community and may account for some failures, as pointed out in our study, in care, and this can be corrected by increasing access to education about AATD and by preforming routine quality-assurance programs.

This study was not without limitations. To begin with, these collected data were only what had been documented in the EHR. At times, patients may receive testing, assessments, and vaccinations from external facilities or health-care professionals, which are not documented in the system's EHR. This may be one of the reasons that multispecialty care may have been missed in our study. Some patients had an "unknown" genotype because their EHR charts state that they had previous abnormal genetic testing, but ambiguous patient histories, discrepancies, and missing laboratory results prevented the specific genotype to be accurately analyzed. Moreover, some patients defer or decline treatment, including vaccinations and testing, which may alter the appearance of proficiency of specialists' ability to manage this rare disease.

Some more definitive treatments, such as liver transplantation in youth, were not considered and may be a source of bias, particularly for patients cared for by a gastroenterologist . In addition, the patient sample size was small due to the rarity of AATD, especially the severe ZZ genotype. Two important outcomes, which should be recommended but we were not able to search, are advanced directives and screening of family members. Both items are essential in the care of a patient with AATD. Importantly, patient care is not isolated; teams work together to provide care to their patients and external consultants may be managing an aspect of the care that is again not documented in the system's EHR. An example is in reaching out to pulmonary specialists for assessment of oxygen desaturation and a 6-minute walk test, which was one of the outcomes that we did not assess in our study. We truly believe that multispecialty teamwork provides the best care for patients with AATD, but this does not remove the need for allergists to screen for AATD, nor, if wanted, manage the disease.

Interestingly, unlike care specified for COPD,[16] which includes patients with AATD, almost all patients who were managed by allergists were on ICS. This may suggest that the patients may express an "asthma phenotype" or "T-helper type 2 phenotype" and present to allergists because of rhinitis associated with lung disease or with aeroallergen allergies, blood eosinophil elevation, reversible airway disease, or elevated immunoglobulin E, and may, for these reasons, be placed on ICS.[17,18] Importantly, a high percentage of patients with AATD may have a degree of reversibility,[19] which is similar to COPD without AATD, and may lead to an inappropriate diagnosis of asthma and lead to the use of ICS too early during the disease.[17]

CONCLUSION

Allergists are ideal for managing AATD, including the severe ZZ genotype, and improvements of management should be reassessed by quality-of-care projects to ensure cost-effective and high-quality care. Allergists have the skill set required to care for patients with complex conditions, *e.g.*, AATD, which affects multiple organs and with varied clinical presentations. Of foremost importance is that all patients with COPD and asthma with a component of fixed airway disease should be screened for AATD. Assessment of liver and lung diseases, and consultation of colleagues in pulmonary and gastroenterology when needed, and healthy liver and lung living is essential for all patients with the ZZ genotype. Those who meet the indication for augmentation should be started on α-1 protein to prevent progressive lung disease. Also, analysis of the data suggests that patients enrolled in a comprehensive management and prevention program have improved outcomes.[20]

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